REMARKS/ARGUMENTS

Rejections under 35 USC 112, first paragraph

In the final Office Action mailed June 16, 2006, claims 1-18, 23-24, and 28 were rejected under 35 U.S.C. 112, first paragraph for failing to comply with the written description requirement. It is respectfully submitted that the amendment to claim 1 renders the Section 112 rejection to claims 1-18 and 23-24 moot.

Claim 1 now claims "A pharmaceutical composition comprising metaxalone in a pharmaceutically acceptable solubility-improved form and at least one pharmaceutically acceptable excipient, characterized in that the pharmaceutical composition has enhanced oral bioavailability as compared to the ~~conventional~~ pharmaceutical composition of metaxalone ~~available commercially~~ corresponding to New Drug Application No. 13-217 when they are administered ~~without food~~ to a patient ~~who has fasted~~ on an empty stomach.

The examiner has considered the wording "when administered without food to a patient who has fasted" as not complying with written description. Applicants respectfully disagree. The above amendment to claim 1 is made to facilitate prosecution. The expression "administered without food to a patient who has fasted" simply means "administered to a patient ***on an empty stomach***." The specification on page 1, lines 7-10, page 2, lines 20-24, page 5, lines 28-33, and page 6 lines 1-3 describes the composition of the instant invention being given to a patient having an empty stomach. The example on page 9, lines 11-13 exemplifies that the pharmaceutical composition of the instant invention and the conventional pharmaceutical

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composition of metaxalone available commercially (Skelaxin®) are administered after overnight fast are only illustrative in that they are administered to patients on an empty stomach.

The meaning of "on an empty stomach" is clear to a person of ordinary skill in the art, *i.e.*, when the stomach is substantially empty of food. *See* the enclosed Chapter 63, "Propulsion and Mixing of Food in the Alimentary Tract" in "Textbook of Medical Physiology", A. C. Guyton and J. E. Hall, 10th Edition, 2004, Elsevier, page 728-737 (a copy of which is concurrently submitted in a Supplemental Information Disclosure Statement).

Thus a person of skill in the art would understand that "on an empty stomach" means, for instance, a condition when food has been digested and the chyme substantially emptied from the stomach. A person of ordinary skill in the art is further aware that, for an ordinary adult, this takes approximately 2-4 hours. Please see "Principles of Anatomy and Physiology", G. J. Tortora and S. R. Grabowski, 9th Edition, John Wiley & Sons, Inc., 2000, page 839-840, and "Remington: The science and Practice of Pharmacy", 20th Edition, Volume II, Editor- A. R. Gennaro, Lippincott Williams & Wilkins, 2001, page 1084-1085 (copies of which are concurrently submitted in a Supplemental Information Disclosure Statement).

The description does not require inclusion of any particular time period because the use of the term administration "on an empty stomach" is common in the art. For example, please refer to "Remington: The science and Practice of Pharmacy", 20th Edition, Volume II, Editor- A. R. Gennaro, Lippincott Williams & Wilkins, 2001, page 1147 (a copy of which is concurrently submitted in a Supplemental Information Disclosure Statement), which recites as below:

> The presence of a large meal in the stomach will delay gastric emptying. If a drug that is absorbed in the intestine is ingested with a large meal, the delay in gastric

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> emptying may result in a delay in absorption of the drug. However, the presence of food in the stomach also has been shown to increase absorption of some drugs. For example, the bioavailabilities of the β-adrenergic blocking drugs, propranolol and metoprolol, are enhanced by the presence of food. Therefore, because of the difficulty in predicting the absorption pattern of a drug in the presence of food, **it is usually advisable to administer drugs when the stomach is empty or 30 min prior to meals;** an exception is with drugs that cause GI irritation and nausea." [Emphasis added].

Thus, the above paragraphs explain how the description requirement for claims 1-18 and 23-24 is met. Given that explanation, it is respectfully submitted that the specification more than sufficiently demonstrates that applicants were in possession of the invention as claimed at the time the application was filed.

For clarification, claim 1 has been amended to contain the limitation of claim 28, and claim 28 has been cancelled. The Office Action considered claim 28 directed to a composition, wherein the bioavailability is characterized in relationship to a New Drug Application (NDA) No. 13-217, as not being in the instant specification and thus rejected as failing to comply with the written description requirement. The specification has been amended to clarify that the bioavailability of the pharmaceutical composition of the present invention was compared to that of conventional pharmaceutical composition of metaxalone available commercially (Skelaxin® (corresponding to New Drug Application No. 13-217, 400 mg tablets). No new matter has been added by this amendment to the specification as shown by the following:

- The only commercially available metaxalone composition at the time the instant application was filed was Skelaxin®, which has NDA No. 13-217, a fact known in the art and available on Orange Book listing.

- Skelaxin® and "commercially available metaxalone composition" have been equated with each other and described throughout the specification.
- The disclosure of Skelaxin® inherently discloses NDA No. 13-217.
- The specification need not provide in 'haec verba' support for the language added to the claim. In order to comply with the written description requirement, the specification "need not describe the claimed subject matter in exactly the same terms as used in the claims; it must simply indicate to persons skilled in the art that as of the date the applicant had invented what is now claimed." *All Dental Prodx LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779, 64 USPQ2d 1945, 1948 (Fed. Cir. 2002), quoting *Eiselstein v. Frank*, 52 F.3d at 1038, 34 USPQ2d at 1470 (citing *Vas-Cath*, 935 F.2d at 1562, 19 USPQ2d at 1115, and *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976)).
- The substitution of NDA No. 13-217 is exactly the type of amendment permitted by M.P.E.P. 2163.07 I., which specifies that "a rewording of a passage where the same meaning remains intact is permissible." *In re Anderson*, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973). *See also Scarring Corp. v. Megan, Inc.*, 222 F.3d 1347, 1352-53, 55 USPQ2d 1650, 1654 (Fed. Cir. 2000) (quoted in the M.P.E.P). In *Scarring*, the original disclosure drawn to recombinant DNA molecules utilized the term "leukocyte interferon." After the filing date, a scientific committee abolished the term in favor of "IFN-(a)," since the latter term more specifically identified a particular polypeptide and since the committee found that leukocytes also produced other types of interferon. The court held that the subsequent amendment to the specification and claims substituting the term "IFN-(a)" for "leukocyte interferon" merely renamed the invention and did not constitute new matter.

Rejections under 35 USC 102(e)

Claims 1-2 and 15 stand rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,407,128 to Scaife et al. Claim 1 has been amended to include the limitation of

claim 2. That is, claim 1 now claims "A pharmaceutical composition comprising metaxalone in a pharmaceutically acceptable solubility-improved form and at least one pharmaceutically acceptable excipient, characterized in that the pharmaceutical composition has enhanced oral bioavailability as compared to the pharmaceutical composition of metaxalone corresponding to New Drug Application No. 13-217 when they are administered ~~without food~~ to a patient ~~who has fasted~~ on an empty stomach." As shown above, the pharmaceutical composition in Scaife et al. corresponds to New Drug Application No. 13-217. The claimed pharmaceutical composition of the present application comprises "metaxalone in a pharmaceutically acceptable solubility-improved form" and "has enhanced oral bioavailability as compared to the pharmaceutical composition of metaxalone corresponding to New Drug Application No. 13-217 [i.e., the pharmaceutical composition in Scaife et al.] when they are administered to a patient on an empty stomach." Scaife et al does not disclose metaxalone in a pharmaceutically acceptable solubility-improved form. Thus, claim 1, as amended, is not anticipated by Scaife et al. As shown below, amended claim 1 is also non-obvious over the prior art, and is therefore patentable.

Rejections under 35 USC 103(a)

Claims 1-15 and 27-28 stand rejected as being unpatentable over Scaife et al. in view of Gilis et al. U.S. Patent No. 6,030,988. Claims 16-18 stand rejected as unpatentable over Scaife et al. as applied to claims 1-15 above in view of Cheng et al. U.S. Patent No. 6,099,859. These rejections are respectfully traversed.

Scaife et al. does not teach "A pharmaceutical composition comprising metaxalone in a pharmaceutically acceptable solubility-improved form and at least one pharmaceutically acceptable excipient, characterized in that the pharmaceutical composition has enhanced oral bioavailability as compared to the pharmaceutical composition of metaxalone corresponding to New Drug Application No. 13-217 when they are administered to a patient on an empty stomach." Neither does Scaife et al. teach "A pharmaceutical composition comprising micronized metaxalone" as claimed in claim 3.

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Gilis et al. does not remedy the deficiencies in Scaife et al. The Office Action acknowledges that Gilis et al. does not teach a pharmaceutical composition comprising metaxalone, but contends that Gilis et al. teaches that a micronized formulation of any drug results in enhanced bioavailability. This contention is incorrect.

Gilis et al. discloses that, instead of using cisapride monohydrate, if solid oral dosage forms of certain cisapride salts like tartrate are used, the formulation can be taken independently from the meal. Gilis et al. relates to use of certain salt forms of cisapride like tartrate, sulfate and citrate. The examples in Gilis et al. disclose cisapride tartrate formulations without mentioning the particle size. Example 14 on dissolution studies and Example 15 on bioavailability studies do not show the effect of particle size on bioavailability. The comparison in Gilis et al. is between the cisapride monohydrate and cisapride tartrate formulations. There is no clear disclosure that micronization results in enhanced oral bioavailability.

The disclosure on particle size in Gilis et al. at Col. 5, starting on line 32, states that "tablets or capsules according to the invention comprise salt forms of cisapride, preferably cisapride(L)–tartrate which are preferable in microfine or micronized form for some uses." Emphasis added. Further, Col. 5, starting on line 51, Gilis et al. states that in some cases for instance, when direct compressing of tablets is desired, "it may be useful to use coarser material (than the micronized or microfine material) of the presently described salts of cisapride." Thus, Gilis et al. does not disclose only micronized particles of salts of cisapride but also discloses coarser particles of salt forms of cisapride. The disclosure in Gilis et al. about particle size is related to tabletting problems and not bioavailability problems. Also, col. 6 of Gilis et al. discloses that formulations of micronized material have 50 % of particles which may have diameter larger than 24 μm, and formulations of coarser material have 50 % of particles which may have diameter larger than 50 μm.

There is no guidance or teaching how to modify Scaife et al. with Gilis et al. to obtain the present invention. A person of ordinary skill in the art reading Gilis et al. would not have known whether to use micronized particles or coarser particles and use of particular particle size to obtain a pharmaceutical composition of metaxalone having enhanced oral bioavailability. It is

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clear from above that Gilis et al. does not teach that reducing particle size of cisapride or its salt affects its bioavailability, nevertheless if the examiner were to cite another reference on a specific drug whose bioavailability was enhanced by reducing particle size it would not be apparent or obvious to a person of skill in the art that the same would occur with metaxalone. Given such prior art above, there was no reasonable expectation that metaxalone in a pharmaceutically acceptable solubility-improved form (e.g., micronized metaxalone) would have enhanced oral bioavailability, i.e., both increased rate as well as extent of absorption, as compared to the pharmaceutical composition of metaxalone corresponding to New Drug Application No. 13-217 when they are administered to a patient on an empty stomach.

Bioavailability as referred to in the specification means both the rate and extent to which the active ingredient is absorbed into the systemic circulation from the pharmaceutical composition.

However, whether it is in fact possible to obtain such an enhancement of both rate and extent of absorption of a particular drug cannot be predicted. In other words, if for example one micronized drug shows improved bioavailability, it does not naturally extend or be extrapolated to metaxalone.

For example, "Remington's Pharmaceutical Sciences", 18th Edition, Mack Publishing Company, Easton, Pennsylvania, 1990, page 1437 (a copy of which is concurrently submitted in a Supplemental Information Disclosure Statement) discusses the effect of particle size reduction of drugs on bioavailability, provides the following:

> Increased bioavailability with particle-size reduction also has been observed with griseofulvin. The extent of absorption of an oral dose increased 2.5 times when the surface area was increased approximately sixfold. Micronized griseofulvin permits a 50% decrease in dosage to obtain a satisfactory clinical response.
>
> On the other hand, it was found that with nitrofurantoin there was an optimal average particle size that minimized side effects without affecting therapeutic response. In fact, a commercial product containing large particles is available. For chloramphenicol, particle size has virtually no effect on total absorption but it significantly affects the rate of appearance of peak blood levels of the drug.

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Therefore, different results are obtained with different drugs and a person of skill in the art would not be motivated to reduce the particle size of metaxalone with a reasonable expectation of success that both rate and extent of absorption of metaxalone will be improved when given on an empty stomach.

A person of skill in the art is aware that reduction in particle size can have undesirable effect on drugs. See "Remington's Pharmaceutical Sciences", 18th Edition, Mack Publishing Company, Easton, Pennsylvania, 1990, pp 1437 which recites as below:

> Particle-size reduction may be deleterious for some drug substances. Increasing surface area by milling or other methods may lead to rapid degradation of a compound. Drug substances also may undergo polymorphic transformation during the milling process.
>
> ***
>
> Reduction of particle size also may create adverse responses. For example, fine particles of the prodrug trichloroethyl carbonate were more toxic in mice than regular and coarse particles.

When rejecting a patent application as obvious based on multiple prior art references, the PTO must articulate the motivations for selecting references and combining them together. The motivation-suggestion-teaching test asks not merely what the references disclose, but whether a person of ordinary skill in the art, possessed with the understandings and knowledge reflected in the prior art, and motivated by the general problem facing the inventor, would have been led to make the combination recited in the claims. *In re Kahn*, 441 F.3d 977, 987-88 (Fed. Cir. 2006).

The Office Action's position that citation of Gilis et al. in Scaife et al. is a motivation to combine the two is not correct and the Office Action does not provide support from case law in support of this position. The motivation should be derived from the prior art themselves or from the general knowledge of a person of skill in the art. Even if it is assumed that Examiner's position is correct, it is amply explained herein that obviousness does not flow from a combination of the cited references taken together with general knowledge of a person of skill in the art because they do not provide each and every feature of the invention.

Scaife et al. investigates effect of food on bioavailability of metaxalone and expressly teaches that bioavailability of metaxalone increases when administered with food. One of ordinary skill in the art would not be motivated to go in an opposite direction of Scaife et al.'s teachings and expect to achieve enhanced bioavailability in a pharmaceutically acceptable solubility-improved form as compared to the composition of Scaife et al. when they are administered to a patient on an empty stomach.

The secondary reference Gilis et al. teaches a pharmaceutical composition comprising a certain salt form of cisapride for the treatment of a gastrointestinal disorder without a drug food interaction. As explained above, Gilis et al. in no way suggests that metaxalone in a pharmaceutical composition of present invention would lead to the unexpected result of enhanced bioavailability of metaxalone even when administered without food.

The Office Action rejected applicant's explanation that reliance on Cheng et al. is not proper on the basis that Cheng et al. is cited by Scaife et al. The Office Action, however, presents no supporting case law for this position. In fact the first requirement is that the prior art must disclose at least one element of the claimed invention. Cheng et al. does not do that. Cheng et al. does not disclose any metaxalone composition with enhanced bioavailability or any method for enhancing bioavailability of metaxalone. Cheng et al. does not disclose any drug composition per se with enhanced bioavailability.

Please refer to Table 1 in column 9 of Cheng et al. The AUC values are only a fraction of the reference product, meaning that the bioavailability is actually decreased rather than enhanced. Example 1 in Table 1 has no absorption enhancer. Examples 2 and 3 of Table 1 have sodium lauryl sulphate as the absorption enhancer, however, in spite of that the ratio of AUC and therefore the bioavailability in comparison to AUC for Glucophage®, the reference product (Test/Reference ratio of AUC) was less than 1.

Because Scaife et al. and Gilis et al., or Scaife et al. and Cheng et al. singly or combined, do not teach or suggest each and every feature recited in the amended claims, the claimed invention is novel and non-obvious in view of the prior art. Accordingly, applicants respectfully request that the prior art rejections be withdrawn.

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In view of the foregoing, it is respectfully submitted that the pending claims are in condition for allowance. The Examiner is invited to contact the undersigned should it be deemed helpful to facilitate prosecution of the application.

Respectfully submitted,

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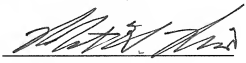
Date: October 13, 2006

By: 

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